REMARKS/ARGUMENTS

As stated above, Applicants elect, with traverse, Group I, claims 2-4 and 7-13, and hydrocortisone as the species, with claims 2-4 and 7-13 readable on the species and claim 11 being generic, for further prosecution and respectfully traverse the requirement for restriction for the following reasons:

It is respectfully submitted that a "therapeutic method for the treatment of ophthalmic diseases by administration of a pharmaceutical composition comprising solid lipidic nanoparticles..." as recited in the Group I claims is sufficiently related to the "pharmaceutical compositions for the treatment of ophthalmic diseases...consisting essentially of an isotonic aqueous dispersion of solid lipid nanoparticles..." as recited in the Group II claims as to warrant examination in a single patent application. The Group II claims are not directed to compositions per se, but rather only to compositions as defined, suitable for the treatment of ophthalmic diseases.

It is respectfully submitted, moreover, that the Examiner's

requirement for a selection of a single species is inappropriate in this case to the extent that it requires Applicants to select a single active substance. It is respectfully submitted that the invention resides in unexpectedly finding that compositions comprising lipidic nanoparticles are able to transport any drug needed by the eye to the vitreous fluid and to the retina. It is respectfully submitted that a means able to convey drugs to the posterior segment of the eye in a simple manner is extremely important and new in that drugs are generally unable to pass the hematoretinic barrier. Of course, the composition of nanoparticles is only a "vector" and the drug must be selected each time accordingly to the therapy to be performed. Nevertheless, it is respectfully submitted that such selection should not justify the selection of a single active substance for purposes of examination of this application.

Moreover, it is believed that any search for the method for the treatment of ophthalmic diseases embodied in Group I, claims 2-4 and 7-13, would necessarily include a search for the compositions as defined in Group II, claims 14-21. Also, it is

believed that any search for the hydrocortisone species would necessarily include a search for the pharmacological active substances embodied in the remaining species. Thus, the simultaneous search for all the groups and species is believed not to constitute an unreasonable search for the Patent Examiner.

In addition, it is believed that the objectives of streamlined examination and compact prosecution would be promoted if a search were conducted simultaneously for all the groups and species. Also, the necessity of filing multiple patent applications in this case does not serve to promote the public interest because of the extra expense that is involved, in filing fees and examination costs, as well as the burden upon the public, due to the necessity of searching through a multiplicity of patent files in order to find the complete range of the subject matter claimed in several different patents that could otherwise be found in one issued patent only.

Applicants reserve the right to file divisional applications for the non-elected Group II and species.

For all these reasons, it is respectfully requested that the restriction requirement under 35 U.S.C. 121 be withdrawn and that an action on the merits of all the claims be rendered.

Respectfully submitted,
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Enclosure: Copy of Merck Index for hydrocortisone (pages 828-829)

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on May 28, 2008.

Amy Klein

Hydrochloride monohydrate. $C_{18}H_{21}NO_3.HCl.H_2O$. Crystals, mp 185-186° dec. $[\alpha]_D^{27}$ −130° (c = 2.877). Very sol in water.

Bitartrate hemipentahydrate. [34195-34-1] Calmodid; Codinovo; Duodin; Kolikodal; Orthoxycol; Mercodinone; Synkonin; Norgan; Hydrokon. $C_{18}H_{21}NO_3.C_4H_6O_6.2½H_2O$; mol wt 494.49. Needles, mp 118-128°. One gram dissolves in 16 ml water, in 150 g 95% ethanol. Almost insol in ether, chloroform. pH of a 2% aq soln about 3.6.

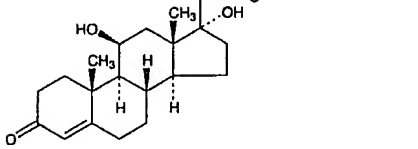
Hydriodide. $C_{18}H_{21}NO_3.HI$. mp 219-220°.

Methiodide. $C_{18}H_{21}NO_3.CH_3I$. mp 250-255°.

Note: This is a controlled substance (opiate): 21 CFR, 1308.12.

THERAP CAT: Analgesic (narcotic); antitussive.

4786. Hydrocortamate. [76-47-1] *N,N*-Diethylglycine (11β)-11,17-dihydroxy-3,20-dioxopregn-4-en-21-yl ester; cortisol 21-ester with *N,N*-diethylglycine; cortisol 21-(*N,N*-diethyl)glycinate; hydrocortisone 21-diethylaminoacetate; Ulcort. $C_{27}H_{41}NO_6$; mol wt 475.62. C 68.18%, H 8.69%, N 2.94%, O 20.18%. Prepn: Pinson, Laubach, DE 1016708 (1957 to Pfizer), *C.A.* **54**, 22737a (1960); Richter, Schenck, DE 1037451 (1958 to Schering AG), *C.A.* **54**, 22730h (1960).

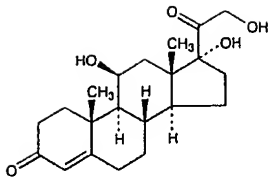


Crystals from ethyl acetate, mp 162-163°.

Hydrochloride. [125-03-1] Ethamicort; Magnacort. $C_{27}H_{41}NO_6.HCl$; mol wt 512.08. Crystals from ethyl acetate, dec 222°.

THERAP CAT: Glucocorticoid.

4787. Hydrocortisone. [50-23-7] (11β)-11,17,21-Trihydroxypregn-4-ene-3,20-dione; cortisol; 4-pregnene-11β,17α,21-triol-3,20-dione; 17-hydroxycorticosterone; anti-inflammatory hormone; Kendall's compound F; Reichstein's substance M; Aerosob-HC; Ala-Cort; Anflam; Cetacort; Cort-Dome; Cortef; Cortenema; Cortril; Dermacort; Dermocortal; Dermolate; Dioderm; Efcortelan; Evacort; Ficortril; Hydracort; Hydro-Adreson; Hydrocort; Hydrocortisyl; Hydrocortone; Hytone; Lacticare-HC; Medicort; Mildison; Nutracort; Penecort; Proctocort; Scheroson F; Synacort; Texacort; Timocort; Zenoxone. $C_{21}H_{30}O_5$; mol wt 362.46. C 69.59%, H 8.34%, O 22.07%. Principal glucocorticoid hormone produced by the adrenal cortex. Biosynthesis stimulated by ACTH, *q.v.* Circulates in plasma primarily bound to ***corticosteroid-binding globulin***, also known as ***transcortin***, and to albumin. Isoln from adrenal glands: Reichstein, *Helv. Chim. Acta* **20**, 953 (1937); Mason *et al.*, *J. Biol. Chem.* **124**, 459 (1938); from urine: Mason, Sprague, *ibid.* **175**, 451 (1948); from blood: Reich *et al.*, *ibid.* **187**, 411 (1950). Configuration: von Euw, Reichstein, *Helv. Chim. Acta* **25**, 988 (1942); **30**, 205 (1947). Synthesis: N. L. Wendler *et al.*, *J. Am. Chem. Soc.* **72**, 5793 (1950). Biosynthesis by isolated adrenal glands: O. Hechter *et al.*, *Arch. Biochem. Biophys.* **25**, 457 (1950); A. Zaffaroni *et al.*, *J. Am. Chem. Soc.* **73**, 1390 (1951). Prepn by microbial transformation: H. C. Murray, D. H. Peterson, US 2602769 (1952 to Upjohn); D. R. Colingsworth *et al.*, *J. Biol. Chem.* **203**, 807 (1953). Total biosynthesis in yeast: F. M. Szczebara *et al.*, *Nat. Biotechnol.* **21**, 143 (2003). Comprehensive description: K. Florey, *Anal. Profiles Drug Subs.* **12**, 277-324 (1983). Review of clinical use in dermatoses: A. M. Kligman, K. H. Knidbey, *Cutis* **22**, 232-244 (1978). Review of clinical assays in serum and urine: A. Moore *et al.*, *Ann. Clin. Biochem.* **22**, 435-454 (1985). Physiological role in immunity: W. M. Jefferies, *Med. Hypotheses* **34**, 198-208 (1991); in fetal maturation: G. C. Liggins, *Reprod. Fertil. Dev.* **6**, 141-150 (1994).



Bitter-tasting crystalline, striated blocks from abs ethanol or isopropanol, mp 217-220° with some decompn. $[\alpha]_D^{22}$ +167° (abs ethanol). uv max: 242 nm ($E_{1cm}^{1\%}$ 445). Soly (mg/ml) at 25°: water 0.28; ethanol 15.0; methanol 6.2; acetone 9.3; chloroform 1.6; propylene glycol 12.7; ether about 0.35. Sol in concd sulfuric acid with intense green fluorescence.

21-Acetate. [50-03-3] Colifoam; Colofoam; Cortaid; Cordes; Cortifoam; Hc45; Hydrocal; Hydrocortistab; Lanacort; Lenirit; Sigmacort; Sintotrat; Velopural. $C_{23}H_{32}O_6$; mol wt 404.50. Monoclinic, sphenoidal, tabular crystals from dil acetone. Tasteless. d_4^{20} 1.289; dec 223°. $[\alpha]_D^{25}$ +166° (c = 0.4 in dioxane); $[\alpha]_D^{25}$ +150.7° (c = 0.5 in acetone). uv max (methanol): 242 nm ($E_{1cm}^{1\%}$ 390). Somewhat hygroscopic. Soly in water: 1 mg/100 ml; in ethanol: 0.45 g/100 ml; in methanol: 3.9 mg/ml; in acetone: 1.1 mg/g; in ether: 0.15 mg/ml. One gram dissolves in about 200 ml chloroform. Very sol in DMF; sol in dioxane.

17-Butyrate. [13609-67-1] Alfason; Laticort; Locoid; Plancol. $C_{25}H_{36}O_6$; mol wt 432.55.

21-Phosphate disodium salt. [6000-74-4] Hydrocortisone sodium phosphate; Cleiton; Efcortesol. $C_{21}H_{29}Na_2O_8P$; mol wt 486.40. White powder. uv max (methanol): 242 nm ($A_{1cm}^{1\%}$ 298-341). $[\alpha]_D^{25}$ +120° (H_2O). Soly in water (25°): >500 mg/ml. pH of a 1% aq soln: 7.5-8.5.

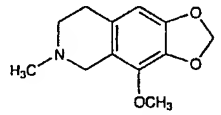
21-Sodium succinate. [125-04-2] Hydrocortisone hemisuccinate sodium salt; A-hydroCort; Buccalsone; Corlan; Efcortelan Soluble; Saxizon; Solu-Cortef; Solu-Glyc. $C_{25}H_{33}NaO_8$; mol wt 484.51. Amorphous, hygroscopic, white powder, mp 169.0-171.2°. Soly in water: ~500 mg/ml. Similarly sol in methanol, ethanol; sparingly sol in chloroform.

17-Valerate. [57524-89-7] Hydrocortisone valerate; Westcort. $C_{26}H_{38}O_6$; mol wt 446.58.

THERAP CAT: Glucocorticoid.

THERAP CAT (VET): Glucocorticoid.

4788. Hydrocotarnine. [550-10-7] 5,6,7,8-Tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-g]isoquinoline; 8-methoxy-5,6-methylenedioxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. $C_{12}H_{15}NO_3$; mol wt 221.25. C 65.14%, H 6.83%, N 6.33%, O 21.69%. Found in mother liquors from morphine extraction. It is not certain whether it is formed from narcotine during the extraction or whether it exists in the poppy plant. May also be prepd by reduction of cotarnine: Topchiev, *J. Appl. Chem. USSR* **6**, 529 (1933), *C.A.* **28**, 2718 (1934); Schneider, Müller, *Ann.* **615**, 34 (1958); Knabe, *Arch. Pharm.* **292**, 652 (1959). Reduction of hydrocotarnine with sodium in alcohol leads to replacement of the methoxyl group by hydrogen, with formation of hydrohydrastinine. Review and bibliography: Small, Lutz, "Chemistry of the Opium Alkaloids," Suppl. No. 103, *Public Health Reports*, Washington (1932).



Hemihydrate. Plates from petr ether, mp 56°. Loses water of crystn at 60°. May be distilled with little decompn at 100°: Hesse, *Ber.* **4**, 693 (1871). Absorption spectrum: Hantzsch, *Ber.* **44**, 1816 (1911); Steiner, *Compt. Rend.* **176**, 244, 1379 (1923); Csokán, *Z. Anal. Chem.* **124**, 344 (1942). Almost insol in water, alkaline solns; sol in alcohol, acetone, chloroform, benzene, ether.

Hydrochloride monohydrate. Prisms; sol in water.

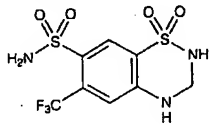
Hydrobromide. Crystals, mp 237°; sparingly sol in water.

Hydriodide. Needles from methanol, mp 196°; sol in hot water.

Methiodide. Needles from water, plates from alc, mp 206°.

Methobromide. Needles from chloroform, dec 221°.

4789. Hydroflumethiazide. [135-09-1] 3,4-Dihydro-6-(trifluoromethyl)-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide; 6-trifluoromethyl-3,4-dihydro-7-sulfamoyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide; 3,4-dihydro-7-sulfamyl-6-trifluoromethyl-1,2,4-benzothiadiazine 1,1-dioxide; trifluoromethylhydrothiazide; dihydroflumethiazide; methforylthiazidine; metfloryltiazidine; Diucardin; Elodrine; Finuret; Hydol; Hydrenox; Leodrine; NaClex; Rodiuran; Rontyl; Saluron; Sisuril; Vergonil. $C_8H_8F_3N_3O_4S_2$; mol wt 331.29. C 29.00%, H 2.43%, F 17.20%, N 12.68%, O 19.32%, S 19.36%. Synthesis: Holdrege *et al., J. Am. Chem. Soc.* **81**, 4807 (1959); Close *et al., ibid.* **82**, 1132 (1960); Yale *et al., ibid.* 2042; Novello *et al., J. Org. Chem.* **25**, 970 (1960). Numerous patents, e.g., Lund *et al.*, US 3254076 (1966 to Lövens Kemiske Fabrik). Pharmacology: J. J. Piala *et al., J. Pharmacol. Exp. Ther.* **134**, 273 (1961). Comprehensive description: C. E. Orzech *et al., Anal. Profiles Drug Subs.* **7**, 297-317 (1978).



Crystals, mp 272-273°. uv max (methanol): 272.5 nm (log ε 4.286). Soly in mg/ml at 25°: acetone >100; methanol 58; acetonitrile 43; water 0.3; ether 0.2; benzene <0.1. pK_1 8.9; pK_2 10.7. Forms water-sol salts with bases. LD_{50} in mice (mg/kg): >8000 orally, 750 i.v., 6280 i.p. (Piala).

THERAPCAT: Antihypertensive; diuretic.

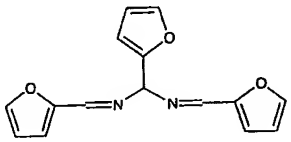
4790. Hydrofluoric Acid. [7664-39-3] Fluohydric acid. HF; mol wt 20.01. Soln of hydrogen fluoride gas in water. Obtained by distilling calcium fluoride with H_2SO_4. Vapor pressure data: Brosheer *et al., Ind. Eng. Chem.* **39**, 423 (1947). Compn of liq and vapor: Munter *et al., ibid.* 427. Review of toxicology and human exposure: *Toxicological Profile for Fluorides, Hydrogen Fluoride, and Fluorine* (PB2004-100002, 2003) 404 pp. *See also* Hydrogen Fluoride.

Colorless or almost colorless, fuming liquid. *Poisonous! Handle with care.* Miscible with water. Weak acid; pKa 3.19. The 38.2% (w/w HF) soln is a binary azeotrope; bp 112.2°. Attacks glass or stoneware, dissolving the silica. *Keep in plastic, lead, wax, or paraffin paper bottles.* Has been marketed in concns of about 47% and 53%. d 1.15-1.18.

Caution: Potential symptoms of overexposure are pulmonary edema, skin and eye burns, rhinitis, bronchitis, bone changes. Direct contact may cause irritation of eyes, skin, nose and throat. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 2003) p 168. *See also Patty's Industrial Hygiene and Toxicology* vol. 2B, G. D. Clayton, F. E. Clayton, Eds. (Wiley-Interscience, New York, 3rd ed., 1981) pp 2945-2948.

USE: Cleaning cast iron, copper, brass; removing efflorescence from brick and stone, or sand particles from metallic castings; working over too heavily weighted silks; frosting, etching glass and enamel; polishing crystal glass; decomposing cellulose; enameling and galvanizing iron; increasing porosity of ceramics. Its salts are used as insecticides and to arrest undesirable fermentation in brewing. Also used in analytical work to determine SiO_2, etc.

4791. Hydrofuramide. [494-47-3] 1-(2-Furanyl)-*N,N'*-bis(2-furanylmethylene)methanediamine; *N,N'*-difurfurylidene-2-furanmethanediamine; furfuramide. $C_{15}H_{12}N_2O_3$; mol wt 268.27. C 67.16%, H 4.51%, N 10.44%, O 17.89%. Prepn: Hartley, Dobbie, *J. Chem. Soc.* **73**, 598 (1898); Taniyama, *J. Chem. Soc. Jpn. Ind. Chem. Sect.* **51**, 33 (1948); Kapur *et al., J. Sci. Ind. Res.* **19B**, 509 (1960); Kamal *et al., Tetrahedron* **19**, 869 (1963). Structure: Soundararajan, Anantakrishnan, *Proc. Indian Acad. Sci.* **38A**, 176 (1953).



Brownish crystals from abs alcohol, mp 117°, bp ~250° with decompn. uv max: 259, 215 nm (log ε 4.18, 4.16). Practically insol in water; freely sol in alc, ether; readily dec by acids.

USE: Vulcanization accelerator.

4792. Hydrogen. [1333-74-0] Protium. H; at. wt 1.00794; at. no. 1; valence 1. Group IA (1). Elemental state: H_2. Exists in two forms, distinguished by the nuclear spins of the atoms: *ortho* has parallel spins, *para* has antiparallel spins. Normal hydrogen is a 3:1 equilibrium ratio of *ortho* to *para* at rm temp. Naturally occurring isotopes: 1 (protium 99.985%); 2 (deuterium 0.015%); 3 (tritium, traces only). The most abundant element in the known universe. Occurrence in the earth's atmosphere 0.00005% H_2. First recognized as an element by Cavendish in 1766; named by Lavoisier. Obtained by passing H_2O vapors over heated iron; by electrolysis of water or by action of HCl or H_2SO_4 on Fe or Zn; by hydrolysis of metal hydrides. Produced industrially by steam reforming, partial oxidation, coal gasification and water electrolysis. *Reviews: Nouveau Traité de Chimie Minérale* vol. 1, P. Pascal, Ed. (Masson, Paris, 1956) pp 565-675; Mackay in *Comprehensive Inorganic Chemistry* vol. 1, J. C. Bailar, Jr. *et al.*, Eds. (Pergamon Press, Oxford, 1973) pp 1-76; *Chemistry of the Elements* N. N. Greenwood, A. Earnshaw, Eds. (Pergamon Press, New York, 1984) pp 38-74; T. A. Czuppon *et al.* in *Kirk-Othmer Encyclopedia of Chemical Technology* vol. 13 (Wiley-Interscience, New York, 4th ed., 1995) pp 838-894. *See also* Deuterium and Tritium.

Colorless, odorless, tasteless gas; flammable or explosive when mixed with air, oxygen, chlorine, etc. mp −259.2° (13.96 K) at 54 mm (triple point). bp −252.77° (20.39 K). d_{gas} 0.069 (air = 1); d_{liq} 0.0700 (at bp); d_{sol} 0.0763 (13 K). A liter of the gas at 0° weighs 0.08987 g. Crit. temp −239.9°; crit press. 12.8 atm. Sol in about 50 vols of water at 0°. Ionization potential of H atom 13.59 eV.

Caution: Can act as an asphyxiant by displacing air. *See: Matheson Gas Data Book* (Matheson, 6th ed., Lyndhurst, NJ, 1980) pp 366-371.

USE: In oxy-hydrogen blowpipe (welding) and limelight; autogenous welding of steel and other metals; manuf ammonia, synthetic methanol, HCl, NH_3; hydrogenation of oils, fats, naphthalene, phenol; in balloons and airships; in metallurgy to reduce oxides to metals; in petroleum refining; in thermonuclear reactions (ionizes to form protons, deuterons (D) or tritons (T)). Liq hydrogen used in bubble chambers to study subatomic particles; as a coolant.

4793. Hydrogen Bromide. [10035-10-6] Anhydrous hydrobromic acid. BrH; mol wt 80.91. Br 98.76%, H 1.25%. HBr. Prepd commercially by direct combination of the elements at 375° preferably over a catalyst such as platinized silica gel or platinized asbestos: Richards, Hönigschmid, *J. Am. Chem. Soc.* **32**, 1581 (1910); Smyth, Hitchcock, *ibid.* **55**, 1830 (1933); Schneider, Johnson, *Inorg. Synth.* **1**, 152 (1939). Lab procedure from tetrahydronaphthalene and bromine: Müller, *Monatsh. Chem.* **49**, 29 (1928); Duncan, *Inorg. Synth.* **1**, 151 (1939); Schmeisser in *Handbook of Preparative Inorganic Chemistry* vol. 1, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) pp 282-286. Detailed description of laboratory methods of prepn: Houben-Weyl, *Methoden der organischen Chemie* vol 5/4 (Thieme, Stuttgart, 4th ed., 1960) p 16-20. Review of prepn and properties of HBr and other hydrogen halides: Woolf in *Mellor's* vol. II, Suppl I (originally published as Suppl II, part 1) 724-741 (1956); John in *Bromine and its Compounds*, Z. E. Jolles, Ed. (Ernest Benn, London, 1966) pp 81-105; Downs, Adams in *Comprehensive Inorganic Chemistry* vol. 2, J. C. Bailar, Jr. *et al.*, Eds. (Pergamon Press, Oxford, 1973) pp 1280-1329.

Colorless, corrosive, nonflammable gas. Acrid odor. Fumes in moist air forming clouds which have a sour taste. d 2.71 (air = 1.00). mp −86.9°. bp_{760} −66.8°; $bp_{11.0\ atm}$ −4.8°; $bp_{17.1\ atm}$ 12°; $bp_{30.0\ atm}$ 36°; $bp_{59.2\ atm}$ 70°. Crit temp 89.8°; crit press. 84.5 atm. Sp heat (cal/g/°C): solid (−91°) 0.152; liq 0.176; gas (27°) 0.085. Heat of fusion at mp: 7.44 cal/g. Heat of vaporization at bp: 51.3 cal/g. Freely sol in water: One vol H_2O dissolves 600 vols HBr gas at 0°. Also sol in alc. Soly in organic solvents: Fernandes, *J. Chem. Eng. Data* **17**, 377 (1972); Gerrard, *Chem. Ind. (London)* 1969, 295; Ahmed *et al., J. Appl. Chem.* **20**, 109 (1970). Aq solns are strongly acid. The satd aq soln contains 68.85% HBr at 0° and 66% at 25°. The boiling point of a constant-boiling mixture is 122.5° at 740 mm and 126° at 760 mm. The composition of the constant-boiling mixture is 47.38% HBr at 752 mm. For complete